

# Biological Warfare

## A Historical Perspective

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The deliberate use of microorganisms and toxins as weapons has been attempted throughout history. Biological warfare has evolved from the crude use of cadavers to contaminate water supplies to the development of specialized munitions for battlefield and covert use. The modern development of biological agents as weapons has paralleled advances in basic and applied microbiology. These include the identification of virulent pathogens suitable for aerosol delivery and industrial-scale fermentation processes to produce large quantities of pathogens and toxins. The history of biological warfare is difficult to assess because of a number of confounding factors. These include difficulties in verification of alleged or attempted biological attacks, the use of allegations of biological attacks for propaganda purposes, the paucity of pertinent microbiological or epidemiologic data, and the incidence of naturally occurring endemic or epidemic diseases during hostilities. Biological warfare has been renounced by 140 nations, primarily for strategic and other pragmatic reasons. International diplomatic efforts, including the 1972 Biological Weapons Convention, have not been entirely effective in preventing the enhancement and proliferation of offensive biological warfare programs. The threats posed by biological weapons are likely to continue into the future.

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HUMANS, regrettably, have used available technologies for destructive as well as for beneficial purposes throughout history. Modern attempts to “weaponize” biological toxins such as botulinum and ricin were anticipated by the use of curare and amphibian-derived toxins as arrow poisons by aboriginal South Americans using neolithic technology. Fomites (ie, objects that harbor and can transmit disease agents) have been used to deliberately transmit infectious diseases since antiquity. The study of the history of biological warfare is confounded by several factors. These include difficulties confirming allegations of biological attack, the lack of reliable microbiological and epidemiologic data regarding alleged or attempted attacks, the use of allegations of biological attack for propaganda, and the secrecy surrounding biological weapons programs. However, a review of historical sources demon-

strates that interest in developing biological weapons has persisted throughout history and is likely to continue into the future.

### EARLY ATTEMPTS

Recognition of the potential impact of infectious diseases on armies resulted in the crude use of filth, cadavers, animal carcasses, and contagion as weapons. These have been used to contaminate wells, reservoirs, and other water sources of armies and civilian populations under attack since antiquity, through the Napoleonic era, and into the 20th century.<sup>1</sup> The use of fomites directly against humans has continued, as evidenced by the smearing of pungent sticks with excrement by the Viet Cong in the early 1960s.<sup>2</sup>

One of the earliest recorded attempts of using fomites against a population illustrates the complex epidemiologic issues raised by biological warfare. During the 14th-century siege of Kaffa (now Feodosia, Ukraine), the attacking Tatar force experienced an epidemic of plague. The Tatars attempted to convert their misfortune into an opportunity by catapulting the cadavers of their deceased into the city to initiate a plague epidemic. An outbreak of plague was followed by the retreat of defending forces and the conquest of Kaffa. Ships carrying plague-infected refugees (and possibly rats) sailed to Con-

stantinople, Genoa, Venice, and other Mediterranean ports and are thought to have contributed to the second plague pandemic.<sup>3</sup> However, given the complex ecology and epidemiology of plague, it may be an oversimplification to implicate the biological attack as the sole cause of the plague epidemic in Kaffa. Plague may have been imported into Kaffa by a natural cycle involving sylvatic and urban rodents and their fleas,<sup>4,5</sup> and the population under siege may have been at increased risk of epidemics because of deteriorating sanitation and hygiene. Since plague-transmitting fleas leave cadavers to parasitize living hosts, we would suggest that the corpses catapulted over the walls of Kaffa may not have been carrying competent plague vectors.

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Smallpox was used as a biological weapon against Native Americans in the 18th century. During the French and Indian War (1754-1767), Sir Jeffrey Amherst, commander of British forces in North America, suggested the deliberate use of smallpox to “reduce” Native American tribes hostile to the British.<sup>6</sup> An outbreak of smallpox at Fort Pitt resulted in the generation of fomites and an opportunity to execute Amherst’s plan. On June 24, 1763, Captain Ecuver, one of Amherst’s subordinates, gave blankets and a handkerchief from the smallpox hospital to the Native Americans and recorded in his journal, “I hope it will have the desired effect.”<sup>7</sup> While this adaptation of the Trojan horse ruse was followed by epidemic smallpox among Native American tribes in the Ohio River valley,<sup>8</sup> other contacts between colonists and Native Americans may have contributed to these epidemics.<sup>9</sup> Smallpox epidemics among immunologically naive tribes of Native Americans following initial contacts with Europeans had been occurring for more than 200 years. In addition, the transmission of smallpox by fomites was inefficient compared with respiratory droplet transmission.<sup>9</sup>

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Both of these early attempts at biological warfare illustrate the difficulty of differentiating naturally occurring epidemics from alleged or attempted biological attack. This problem has had continued relevance because naturally occurring endemic diseases have been ascribed to alleged biological attacks for propaganda purposes.

### THE ERA OF MODERN MICROBIOLOGY AND THE USE OF BIOLOGICAL WEAPONS DURING THE WORLD WARS

The formulation of Koch's postulates and the development of modern microbiology during the 19th century afforded the capability to isolate and produce stocks of specific pathogens. Substantial evidence suggests that Germany developed an ambitious biological warfare program during World War I, featuring covert operations in neutral trading partners of the Allies to infect livestock and contaminate animal feed to be exported to Allied forces.<sup>10</sup> *Bacillus anthracis* and *Burkholderia (Pseudomonas) mallei*, the etiologic agents of anthrax and glanders, were to be used to infect Romanian sheep for export to Russia. Cultures confiscated from the German Legation in Romania in 1916 were identified as *B anthracis* and *B mallei* at the Bucharest Institute of Bacteriology and Pathology.<sup>4,5</sup> *Burkholderia mallei* was allegedly used by German saboteurs operating in Mesopotamia to inoculate 4500 mules and in France to infect horses of the French cavalry.<sup>4</sup> Argentinian livestock intended for export to Allied forces were infected with *B anthracis* and *B mallei*, resulting in the deaths of more than 200 mules from 1917 to 1918.<sup>4</sup> Operations in the United States included attempts to contaminate animal feed and to infect horses intended for export during World War I.<sup>11</sup>

In response to the horror of chemical warfare during World War I, international diplomatic efforts were directed toward limiting the proliferation and use of weapons of mass destruction. The first diplomatic attempt at limiting biological warfare was the 1925 Geneva Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare.<sup>12</sup> This treaty prohibited the use of biological weapons. However, the treaty did not proscribe basic research, production, or possession of biological weapons, and many countries ratified the protocol while stipulating a right of retaliation.<sup>12</sup> There were no provisions for inspection. Parties to the Geneva Protocol that began basic research programs to develop biological weapons after World War I included Belgium, Canada, France, Great Britain, Italy, the Netherlands, Poland, and the Soviet

Union.<sup>13</sup> The United States did not ratify the Geneva Protocol until 1975.

Japan conducted biological weapons research in occupied Manchuria from 1932 until the end of World War II under the direction of Shiro Ishii (1932-1942) and Kitano Misaji (1942-1945). Unit 731, a biological warfare research facility located near the town of Pingfan, was the center of the Japanese biological weapons development program and contained 150 buildings, 5 satellite camps, and a staff of more than 3000 scientists and technicians. Additional units were located at Mukden, Changchun, and Nanking. Prisoners were infected with pathogens including *B anthracis*, *Neisseria meningitidis*, *Shigella* spp, *Vibrio cholerae*, and *Yersinia pestis*.<sup>13,14</sup> At least 10 000 prisoners died as a result of experimental infection or execution following experimentation during the Japanese program between 1932 and 1945.<sup>14</sup>

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Participants in the Japanese program who had been captured by the Soviet Union during World War II admitted to 12 large-scale field trials of biological weapons in testimony obtained during war crimes prosecution.<sup>15,16</sup> At least 11 Chinese cities were attacked with biological agents. Attacks featured contaminating water supplies and food items with pure cultures of *B anthracis*, *V cholerae*, *Shigella* spp, *Salmonella* spp, and *Y pestis*. Cultures were also tossed directly into homes and sprayed from aircraft.<sup>13-16</sup> Plague was allegedly developed as a biological weapon by allowing laboratory-bred fleas to feed on plague-infected rats. These potentially infected fleas were then harvested and released from aircraft over Chinese cities. As many as 15 million fleas were released per attack to initiate epidemics of plague. Dr P. Z. King, director general of the Chinese National Health Administration, attributed epidemic plague to these attacks; however, rigorous epidemiologic and bacteriologic data are not available.<sup>17</sup> In addition, the Japanese had not adequately prepared, trained, or equipped their own troops for the hazards of biological weapons. An attack on Changteh in 1941 reportedly led to approximately 10 000 biological casualties and 1700 deaths among Japanese troops, with most cases due to cholera.<sup>16</sup> Field trials were terminated by Misaji in 1942, although basic research continued until the end of the war.<sup>14</sup>

Hitler reportedly issued orders prohibiting biological weapons development in

Germany. However, with the support of high-ranking Nazi party officials, German scientists began biological weapons research, although their results lagged far behind those of other countries. A German offensive biological weapons threat never materialized.<sup>18</sup> Prisoners in Nazi concentration camps were forcibly infected with *Rickettsia prowazekii*, *Rickettsia mooseri*, hepatitis A virus, and *Plasmodium* spp and treated with investigational vaccines and drugs. These inhumane experiments were done to study pathogenesis, to develop vaccines against rickettsiae, and to develop sulfonamides rather than to develop biological weapons.<sup>18</sup> The only known German tactical use of biological warfare was the pollution of a large reservoir in northwestern Bohemia with sewage in May 1945.<sup>1</sup> Ironically, the combination of a vaccine and a serologic test was used as a biological defense against the Nazis. The German army avoided areas with epidemic typhus by using the Weil-Felix reaction for diagnosis. Consequently, physicians used formalin-killed *Proteus* OX-19 as a vaccine to induce biological false-positive tests for typhus in an area of occupied Poland, and residents were protected from deportation to concentration camps.<sup>19</sup>

The Allies developed biological weapons for potential retaliatory use in response to German biological attack. Bomb experiments of weaponized spores of *B anthracis* were conducted on Gruinard Island near the coast of Scotland and resulted in heavy contamination. Viable anthrax spores persisted until the island was decontaminated with formaldehyde and seawater during 1986.<sup>20</sup>

### THE US PROGRAM

In the United States, an offensive biological program was begun in 1942 under the direction of a civilian agency, the War Reserve Service. The program included a research and development facility at Camp Detrick, Md (renamed Fort Detrick in 1956), testing sites in Mississippi and Utah, and a production facility in Terre Haute, Ind. Experiments were conducted using pathogens, including *B anthracis* and *Brucella suis*. However, the production facility lacked adequate engineering safety measures. For example, tests of the fermentation and storage processes using nonpathogenic *Bacillus subtilis* var *globigii* as a *B anthracis* simulant disclosed contamination of the plant and environs. These findings precluded large-scale production of biological weapons during World War II, although 5000 bombs filled with *B anthracis* spores were produced at a pilot plant at Camp Detrick.<sup>21</sup> After the war, the production facility was leased and converted to commercial pharmaceutical production.<sup>21</sup> Basic research and develop-

ment activities were continued at Camp Detrick. Ishii, Misaji, and other Japanese scientists in American custody who had participated in the Unit 731 program were granted immunity from war crimes prosecution on the condition that they would disclose information obtained during their program. Secret debriefings were conducted during the postwar era.<sup>13,16</sup>

The US program was expanded during the Korean War (1950-1953). A new production facility incorporating adequate biosafety measures was constructed at Pine Bluff, Ark. Technical advances allowed large-scale fermentation, concentration, storage, and weaponization of microorganisms; production was begun in 1954. In addition, a program to develop countermeasures, including vaccines, antisera, and therapeutic agents to protect troops from possible biological attack, was begun in 1953.

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Animal studies were performed at Fort Detrick, at remote desert sites, and on barges in the Pacific Ocean. Human experimentation using military and civilian volunteers was initiated in 1955. Biological munitions were detonated inside a 1-million-liter, hollow, metallic, spherical aerosolization chamber at Fort Detrick known as the "eight ball." Volunteers inside the chamber were exposed to *Francisella tularensis* and *Coxiella burnetii*. These and other challenge studies were done to determine vulnerability to aerosolized pathogens and the efficacy of vaccines, prophylaxis, and therapies under development. Additional studies were done using simulants. *Aspergillus fumigatus*, *B subtilis* var *globigii*, and *Serratia marcescens* were selected for use as simulants; these organisms were thought to be nonpathogenic and were used to study production and storage techniques as well as aerosolization methods, the behavior of aerosols over large geographic areas, and the effects of solar irradiation and climatic conditions on the viability of aerosolized organisms. Cities were surreptitiously used as laboratories to test aerosolization and dispersal methods when simulants were released during covert experiments in New York City, San Francisco, and other sites between 1949 and 1968.<sup>21,22,23</sup>

Concerns regarding potential public health hazards of simulant studies were raised after an outbreak of urinary tract infections caused by nosocomial *S marcescens* (formerly *Chromobacterium prodigiosum*) occurred at Stanford Univer-

sity Hospital between September 1950 and February 1951.<sup>24</sup> The outbreak followed covert experiments using *S marcescens* as a simulant in San Francisco.<sup>23</sup> The outbreak involved 11 cases, resulting in 1 transient bacteremia and 1 death from endocarditis. All patients had undergone urinary tract catheterization, and 5 had undergone cystoscopy for urologic indications. Exposure to multiple antibiotics was cited as a contributing factor to the outbreak.<sup>24</sup> No similar outbreaks were reported by other hospitals in the San Francisco area. This outbreak is thought to represent an early example of nosocomial epidemics caused by opportunists of low virulence, related to antibiotic use, new medical devices, and surgical procedures.<sup>25</sup>

In view of the temporal relationship of the outbreak with the simulant studies, the army convened an investigative panel in 1952, including members from the Communicable Disease Center, the National Institutes of Health, the City of New York Health Department, and Ohio State University. The panel did not comment directly on the possible association of the nosocomial outbreak and the simulant studies. The panel recommended continued use of *S marcescens* in view of its low virulence, but added that a search for better simulants to replace *S marcescens* should be pursued.<sup>23</sup> However, simulant studies using *S marcescens* continued until 1968. Public interest in these covert experiments was aroused in 1976 when the *Washington Post* reported them<sup>26</sup> and implied that the endocarditis death was a direct result of the simulant testing. It was further implied that sudden increases in the incidence of pneumonia in Calhoun County, Alabama, and Key West, Fla, were related to simulant studies at those locales. As a result of the ensuing public outcry, Senate hearings were held in 1977, and the army was severely criticized for the continued use of *S marcescens* following awareness of the Stanford outbreak.<sup>22</sup>

Nonetheless, several facts cast doubt on an etiologic relationship between military use of *S marcescens* and outbreaks of human disease. The Centers for Disease Control reported that in 100 outbreaks of *S marcescens* infection, none was caused by the 8UK strain used by the army (biotype A6, serotype O8:H3, phage type 678).<sup>27</sup> Numerous reports during the 1970s postulated a link between the army experiments and cases of *S marcescens* endocarditis, septic arthritis, and osteomyelitis in California heroin addicts; where strains were available for testing, they were likewise shown to differ antigenically from the army test strain.<sup>27</sup> A review of the role of *S marcescens* in the army biological program was published in 1979.<sup>25</sup>

Table 1.—Biological Agents Weaponized and Stockpiled by the US Military (Destroyed 1971-1973)

Lethal agents*
<i>Bacillus anthracis</i>
Botulinum toxin
<i>Francisella tularensis</i>
Incapacitating agents*
<i>Brucella suis</i>
<i>Coxiella burnetii</i>
Staphylococcal enterotoxin B
Venezuelan equine encephalitis virus
Anticrop agents†
Rice blast
Rye stem rust
Wheat stem rust

\*Weaponized.

†Stockpiled, but not weaponized.

There were 456 cases of occupational infections acquired at Fort Detrick during the offensive biological program (1943-1969), at a rate of less than 10 infections per 1 million hours worked. The rate of occupational infection was well within the contemporary standards of the National Safety Council and below the rates reported from other laboratories. There were 3 fatalities due to occupationally acquired infections—2 cases of anthrax in 1951 and 1958 and a case of viral encephalitis in 1964. The mortality rate was lower than those of other contemporary surveys of laboratory-acquired infections. There were 48 occupational infections and no fatalities reported from production and testing sites. The safety program included the development and use of new vaccines as well as engineering safety measures.<sup>23</sup>

By the late 1960s, the US military had developed a biological arsenal that included numerous bacterial pathogens, toxins, and fungal plant pathogens that could be directed against crops to induce crop failure and famine (Table 1).<sup>23</sup> In addition, weapons for covert use using cobra venom, saxitoxin, and other toxins were developed for use by the Central Intelligence Agency; all records regarding their development and use were destroyed during 1972.<sup>28</sup>

## KOREAN WAR AND COLD WAR ALLEGATIONS

The Soviet Union, China, and North Korea accused the United States of using biological warfare against North Korea and China during the Korean War. These accusations were supported by a series of investigations conducted by the International Scientific Commission, a group of scientists, and other organizations not part of the commission. Although these investigations were described as impartial, they were carefully controlled by the North Korean and Chinese governments.<sup>29</sup> The United States admitted to having biological warfare capabilities, but denied using biological weapons. The United States requested impartial investigations. The Interna-

tional Committee of the Red Cross suggested the formation of a special commission to investigate, and the World Health Organization offered to intervene. Neither China nor North Korea responded to the International Committee of the Red Cross, and the World Health Organization's offer was rebuffed as a disguised attempt at espionage. Consequently, the United States and 15 other nations submitted a resolution to the United Nations (UN) requesting the formation of a neutral commission to investigate the allegations; however, implementation of the resolution was prevented by the Soviet Union. The credibility of the United States was undermined by its failure to ratify the 1925 Geneva Protocol, by knowledge of its offensive biological warfare program, and the suspected covert collaboration with the Unit 731 scientists.<sup>29</sup> Although unsubstantiated, the accusations of US use of biological weapons attracted wide attention and resulted in a loss of international goodwill toward the United States. This episode demonstrated the propaganda value of biological warfare allegations, regardless of veracity.<sup>29,30</sup>

Numerous unsubstantiated allegations were made during the cold war era. These included Soviet accusations of US biological weapons testing against Canadian Eskimos resulting in a plague epidemic<sup>31</sup> and of a US and Columbian biological attack on Columbian and Bolivian peasants.<sup>32</sup> The United States also was accused of planning to initiate an epidemic of cholera in southeastern China<sup>33</sup> and of the covert release of dengue in Cuba.<sup>34</sup>

Similarly, the US allegations that Soviet armed forces and their proxies had used aerosolized trichothecene mycotoxins ("yellow rain"), potent inhibitors of DNA and protein synthesis derived from fungi of the genus *Fusarium*, in Laos (1975-1981), Kampuchea (1979-1981), and Afghanistan (1979-1981) are widely regarded as erroneous. The remote locations of the alleged attacks made intelligence investigations extremely difficult. Attacks were never witnessed by Western intelligence operatives, and samples of the aerosols were not recovered. Confounding factors included the following: contradictory testimonies from survivors of the alleged attack, discrepancies in reported symptoms, low disease rates in the allegedly exposed populations, the recovery of mycotoxin in less than 10% of the clinical and environmental samples submitted, the presence of *Fusarium* organisms as environmental commensals, the possible decay of toxin under prevailing environmental conditions, conflicting results of toxin assays from different laboratories, the similarity of alleged yellow rain deposits recovered from environ-

mental surfaces to bee feces in ultrastructural appearance and pollen and mold content, and the natural occurrence of showers of bee feces from swarms of honey bees in the rain forests of southeast Asia.<sup>35</sup>

### DISARMAMENT EFFORTS

During the late 1960s, there was increasing international concern regarding the indiscriminate nature, unpredictability, epidemiologic risks, and lack of epidemiologic control measures for biological weapons, as well as the ineffectiveness of the 1925 Geneva Protocol for preventing biological weapons proliferation. In July 1969, Great Britain submitted a proposal to the Committee on Disarmament of the UN prohibiting the development, production, and stockpiling of biological weapons and providing for inspections in response to alleged violations. During the following September, the Warsaw Pact nations submitted a biological disarmament proposal similar to the British proposal, but without provisions for inspections. Two months later, the World Health Organization issued a report regarding the potential consequences of biological warfare.<sup>36</sup> Estimates of the casualty figures that could result from biological attacks were staggering (Table 2).<sup>36</sup>

Subsequently, the 1972 Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction (BWC) was developed.<sup>37</sup> The treaty prohibits the development, possession, and stockpiling of pathogens or toxins in "quantities that have no justification for prophylactic, protective or other peaceful purposes." The BWC also prohibits the development of delivery systems intended to disperse biological agents and requires parties to destroy stocks of biological agents, delivery systems, and equipment within 9 months of ratifying the treaty. Transferring biological warfare technology or expertise to other countries is also prohibited. Signatories that have not yet ratified the BWC are obliged to refrain from activities that would defeat the purpose of the treaty until they explicitly communicate their intention not to ratify. However, there are unresolved controversies regarding the quantities of pathogens required for benevolent research and the definition of "defensive" research. Allegations of infractions may be lodged with the UN Security Council, which may in turn initiate inspections of accused parties; however, this provision is undermined by the right of Security Council members to veto proposed inspections.

The treaty was ratified in April 1972 and went into effect in March 1975. There were more than 100 signatory nations, including Iraq and the members of the Se-

Table 2.—Estimates of Casualties Produced by Hypothetical Biological Attack\*

Agent	Downwind Reach, km	No. Dead	No. Incapacitated
Rift Valley fever	1	400	35 000
Tick-borne encephalitis	1	9500	35 000
Typhus	5	19 000	85 000
Brucellosis	10	500	125 000
Q fever	>20	150	125 000
Tularemia	>20	30 000	125 000
Anthrax	>20	95 000	125 000

\*Release of 50 kg of agent by aircraft along a 2-km line upwind of a population center of 500 000.<sup>36</sup>

curity Council (which included the United States and the Soviet Union). Review conferences were held in 1981, 1986, 1991, and 1996. Annual reports regarding biological research facilities, scientific conferences held at specified facilities, scientific exchanges, and epidemics are submitted to the UN as an additional confidence-building measure.<sup>37</sup>

President Nixon terminated the US offensive biological weapons program by executive order in 1969 and 1970. The United States adopted a policy never to use biological weapons, including toxins, under any circumstances whatsoever. National Security Decisions 35 and 44, issued during November 1969 (microorganisms) and February 1970 (toxins), mandated the cessation of offensive biological research and production and the destruction of the biological arsenal. Research efforts were directed exclusively to the development of defensive measures such as diagnostic tests, vaccines, and therapies for potential biological weapons threats. Stocks of pathogens and the entire biological arsenal were destroyed between May 1971 and February 1973 under the auspices of the US Department of Agriculture, the US Department of Health, Education, and Welfare, and the Departments of Natural Resources of Arkansas, Colorado, and Maryland. Small quantities of pathogens were retained at Fort Detrick to test the efficacy of investigational preventive measures and therapies. The Central Intelligence Agency was admonished during a 1975 congressional hearing for illegally retaining samples of toxins after presidential orders mandating their destruction.<sup>28</sup>

While many welcomed the termination of the US offensive program for moral and ethical reasons, the decision to terminate the offensive biological program was motivated by pragmatic considerations. Given the available conventional, chemical, and nuclear weapons, biological weapons were not considered essential for national security. The potential effects of biological weapons on military and civilian populations were still conjectural, and for obvious ethical and public health reasons could not be empirically studied. Biological weapons were considered untried,

unpredictable, and potentially hazardous for the users as well as for those under attack. Field commanders and troops were unfamiliar with their use. In addition, the United States and allied countries had a strategic interest in outlawing biological weapons programs to prevent the proliferation of relatively low-cost weapons of mass destruction. By outlawing biological weapons, the arms race for weapons of mass destruction would be prohibitively expensive, given the expense of nuclear programs.<sup>38</sup>

After the termination of the offensive biological program, the US Army Medical Research Institute of Infectious Diseases (USAMRIID) was established to continue the development of medical defenses for the US military against potential biological attack. The mission of USAMRIID is to conduct research to develop strategies, products, information, and training programs for medical defense against potential biological weapons. Endemic or epidemic infectious diseases due to highly virulent pathogens requiring high-level containment for laboratory safety are also studied. The USAMRIID is an open research institution; no research is classified. The in-house programs are complemented by contract programs with universities and other research institutions.

#### FOLLOWING THE 1972 BWC

Several signatory nations of the 1972 BWC, including Iraq and the former Soviet Union, have participated in activities outlawed by the convention. These events demonstrate the ineffectiveness of the convention as the sole means for eradicating biological weapons and preventing further proliferation.

Biological weapons were used for covert assassination during the 1970s. Ricin, a lethal toxin derived from castor beans, was weaponized by the secret service of the Soviet Union and deployed by the Bulgarian secret service. Metallic pellets that were 1.7 mm in diameter were cross drilled, filled with ricin, and sealed with wax intended to melt at body temperature. The pellets were discharged from spring-powered weapons disguised as umbrellas. These weapons were used to assassinate Georgi Markov, a Bulgarian defector living in London, and during an unsuccessful assassination attempt against another defector, Vladamir Kostov, in 1978. Similar weapons may have been used for at least 6 other assassinations.<sup>39</sup>

An epidemic of anthrax occurred during April 1979 among people who lived or worked within a distance of 4 km in a narrow zone downwind of a Soviet military microbiology facility in Sverdlovsk (now Ekaterinburg, Russia). In addition, livestock died of anthrax along the extended axis of the epidemic zone out to a

distance of 50 km.<sup>40</sup> The facility was suspected by Western intelligence of being a biological warfare research facility, and the epidemic was attributed by Western analysts to the accidental airborne release of anthrax spores.

The Soviets maintained that the epidemic was caused by ingestion of contaminated meat purchased on the black market. In 1992, Boris Yeltsin, the president of Russia, admitted that the facility had been part of an offensive biological weapons program and that the epidemic had been caused by a nonintentional release of anthrax spores.<sup>41</sup> It was determined that air filters had not been activated early on the morning of April 3.<sup>42</sup> Inhalation anthrax was identified at autopsy as the cause of death in victims.<sup>43</sup> At least 77 cases and 66 deaths occurred, constituting the largest documented epidemic of inhalation anthrax in history.<sup>42</sup> The Soviets continued an offensive biological warfare program after the BWC of 1972 under the aegis of Biopreparat, an organization under the Ministry of Defense.<sup>44</sup> During the 1970s and 1980s, Biopreparat operated at least 6 research laboratories and 5 production facilities and employed up to 55 000 scientists and technicians.<sup>45</sup> The extensive program of the former Soviet Union is now controlled largely by Russia. Yeltsin stated in 1992 that he would end further offensive biological research and production<sup>41</sup>; however, the degree to which the program has been reduced is not known. A 1995 report estimated that the Russian program continues to employ 25 000 to 30 000 people.<sup>45</sup>

Before the Persian Gulf War, intelligence reports suggested that the Iraqi regime had sponsored an ambitious biological warfare program. Coalition forces prepared for potential biological warfare by training in protective masks and equipment, reviewing decontamination procedures, and immunizing troops against potential biological warfare threats. Approximately 150 000 US troops received a Food and Drug Administration–licensed toxoid vaccine against anthrax, and 8000 received a botulinum toxoid vaccine approved by the Food and Drug Administration as an Investigational New Drug. In addition, 30 million 500-mg oral doses of ciprofloxacin were stockpiled in the theater of operations to provide a 1-month course of chemoprophylaxis for the 500 000 US troops in the event that anthrax spores were used as a biological weapon.

Information regarding the Iraqi offensive biological program was obtained after the Persian Gulf War during UN weapons inspections. Iraqi officials admitted to having had an offensive biological weapons program that included basic research on *B anthracis*, rotavirus, camel

pox virus, aflatoxin, botulinum toxins, mycotoxins, and an anticrop agent (wheat cover rust).<sup>46,47</sup> Fortunately, biological weapons were not used during the Persian Gulf War. The Iraqi government claims to have destroyed its biological arsenal after the war. Research and production facilities that had escaped destruction during the war were demolished by the UN Special Commission on Iraq (UNSCOM) in 1996. The Persian Gulf War and postwar findings have led to a recent decision by the US military to develop a plan to immunize troops against anthrax.<sup>48</sup>

The biological threat posed by nonstate-sponsored terrorists was demonstrated by the intentional contamination of salad bars in Oregon restaurants with *Salmonella* Typhimurium by the Rajneeshee cult during late September 1984. This incident resulted in 751 cases of enteritis and 45 hospitalizations. Although the Rajneeshees were suspected, and despite rigorous epidemiologic analyses by the Wasco-Sherman Public Health Department, the Oregon State Health Division, and the Centers for Disease Control,<sup>49,50</sup> the origin of the epidemic as a deliberate biological attack was not confirmed until a cult member admitted to the attack in 1985.<sup>51,52</sup>

The threat of biological terrorism resurfaced following the Aum Shinrikyo sarin attack of the Tokyo subway system in March 1995. Police raids and investigations of the cult's facilities disclosed evidence of a rudimentary biological weapons program. The cult was allegedly conducting research of *B anthracis*, *Clostridium botulinum*, and *C burnetii*. The cult's arsenal seized by police allegedly contained botulinum toxin and drone aircraft equipped with spray tanks.<sup>53</sup> The cult had allegedly launched 3 unsuccessful biological attacks in Japan using *B anthracis* and botulinum toxin and had sent members to the former Zaire during 1992 to obtain Ebola virus for weapons development.<sup>54</sup>

#### CONCLUSIONS

Allegations of biological attacks have been made since World War I. However, most of these have not been confirmed in the absence of compelling microbiological or epidemiologic data supporting a biological attack. Furthermore, the Rajneeshee incident in Oregon demonstrated that biological attacks may be easy to conceal despite state-of-the-art microbiological and epidemiologic analysis. These incidents underscore the difficulty of differentiating biological attacks from naturally occurring epidemics or endemic disease and emphasize the increased risk of epidemics during hostilities because of deteriorating hygiene, sanitation, and public health infrastructure. The practice of ascribing

naturally occurring epidemic or endemic diseases to alleged biological attacks for propaganda purposes demonstrates the perception of psychological vulnerability to the threat of biological warfare.

Confirmed incidents involving biological weapons since World War II include the Sverdlovsk accident, the ricin assassination attempts, the Rajneeshee incident, and the discovery of the Aum Shinrikyo biological weapons effort. The most immediate threat of biological warfare to date was posed by Iraq during the Persian Gulf War. The reasons behind Saddam Hussein's decision not to use his biological arsenal are unknown. The most frequently proposed hypothesis forwarded by Western military analysts and intelligence sources has been possible Iraqi concern regarding the risk of provoking massive retaliation. Alternatively, other considerations may have included

the possible ineffectiveness of Hussein's biological weapons and hazards to his own forces because of deficiencies in Iraqi training and equipment.<sup>55</sup>

International agreements to limit biological weapons proliferation have not been completely effective, as evidenced by events in the former Soviet Union and Iraq, both of which demonstrated activities prohibited by the BWC of 1972. Efforts to formulate legally binding measures to verify compliance with the BWC have been undertaken but, as of the Fourth Review Conference in December 1996 in Geneva, Switzerland, such efforts have not been successful. Disagreements continue regarding the utility of routine inspections at biological research facilities and the political, economic, commercial, and security consequences of such inspections. The Ad Hoc Group of Government Experts on Verification will con-

tinue to negotiate measures to verify compliance and is charged to complete its work "as soon as possible," and no later than 2001. A Fifth Review Conference is to be held in 2001.<sup>56,57</sup>

Concern continues regarding the possibility of proliferation or enhancement of state-sponsored, offensive biological weapons programs and the possible use of biological weapons by terrorist organizations. Following the termination of the US offensive program from 1969-1970, biological defense in the US military has focused on the development of countermeasures including detection capabilities, personal protective equipment, vaccines, diagnostics, and therapies to protect our military members.

This article is dedicated to the late Jay P. Sanford, MD, in appreciation for his invaluable contributions to the fields of infectious diseases, military medicine, and medical education.

## References

1. Stockholm International Peace Research Institute (SPIRI). *The Rise of CB Weapons: The Problem of Chemical and Biological Warfare*. New York, NY: Humanities Press; 1971;1.
2. Stubbs M. Has the West an Achilles heel: possibilities of biological weapons. *NATO's Fifteen Nations*. June/July 1962;7:94-99.
3. Derbes VJ. De Mussis and the great plague of 1348: a forgotten episode of bacteriological war. *JAMA*. 1966;196:59-62.
4. Robertson AG, Robertson LJ. From asps to allegations: biological warfare in history. *Mil Med*. 1995;160:369-373.
5. Berdal BP, Omland T. *Biologiske vapen-konvensjoner og historikk*. *Tidsskr Nor Lægeforen*. 1990; 110:736-741.
6. Parkman F. *The Conspiracy of Pontiac and the Indian War After the Conquest of Canada*. Boston, Mass: Little Brown & Co Inc; 1901;2.
7. Sipe CH. *The Indian Wars of Pennsylvania*. Harrisburg, Pa: Telegraph Press; 1929.
8. Stearn EW, Stearn AE. *The Effect of Smallpox on the Destiny of the Amerindian*. Boston, Mass: Bruce Humphries; 1945.
9. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. *Smallpox and Its Eradication*. Geneva, Switzerland: World Health Organization; 1988.
10. Hugh-Jones M. Wickham Steed and German biological warfare research. *Intell Natl Secur*. 1992; 7:379-402.
11. Witcover J. *Sabotage at Black Tom: Imperial Germany's Secret War in America, 1914-1917*. Chapel Hill, NC: Algonquin Books of Chapel Hill; 1989.
12. Geissler E. *Biological and Toxin Weapons Today*. New York, NY: Oxford University Press Inc; 1986.
13. Harris SH. *Factories of Death*. New York, NY: Routledge; 1994.
14. Harris S. Japanese biological warfare research on humans: a case study of microbiology and ethics. *Ann N Y Acad Sci*. 1992;666:21-52.
15. Tomlin VV, Berezhnai RV. Exposure of criminal activity of the Japanese military authorities regarding preparation for biological warfare. *Voen Med Zh*. 1985;8:26-29.
16. Williams P, Wallace D. *Unit 731: Japan's Secret Biological Warfare in World War II*. New York, NY: Free Press; 1989.
17. King PZ. Bacteriological warfare. *Chin Med J*. 1943;61:259-263.
18. Mitscherlich A, Mielke F. *Medizin ohne Menschlichkeit: Dokumente des Nürnberger Ärzteprozesses*. Frankfurt am Main, Germany: Fischer Taschenbuchverlag; 1983.
19. Lazowski ES, Matulewicz S. Serendipitous discovery of artificial Weil-Felix reaction used in 'private immunological war'. *ASM News*. 1977;43:300-302.
20. Manchee RJ, Stewart R. The decontamination of Gruinard Island. *Chem Br*. 1988;24:690-691.
21. Harris R, Paxman JA. *A Higher Form of Killing*. New York, NY: Hill & Wang; 1982.
22. US Congress. *Biological Testing Involving Human Subjects by the Department of Defense, 1977: Hearings before the Subcommittee on Health and Science Research of the US Senate*, 95th Cong, 1st Sess. Washington, DC: US Congress; March 8 and May 23, 1977.
23. US Dept of the Army. *US Army Activity in the US Biological Warfare Programs*. Washington, DC: US Dept of the Army; February 24, 1977;2. Publication DTIC B193427 L.
24. Wheat RP, Zuckerman A, Rantz LA. Infection due to chromobacteria. *Arch Intern Med*. 1951;88:461-466.
25. Yu VL. *Serratia marcescens*: historical perspective and clinical review. *N Engl J Med*. 1979;300: 887-893.
26. *Washington Post*. December 22, 1976.
27. Farmer JJ III, Davis BR, Grimont PAD, Grimont F. Source of American *Serratia*. *Lancet*. 1977; 2:459-460.
28. US Senate. *Unauthorized Storage of Toxic Agents: Hearings before US Senate Intelligence Committee*, 94th Cong, 1st Sess. Washington, DC: US Senate; September 16-18, 1975.
29. Van Courtland Moon JE. The Korean War case. *Ann N Y Acad Sci*. 1992;666:53-83.
30. Rolicka M. New studies disputing allegations of bacteriological warfare during the Korean War. *Mil Med*. 1995;160:97-100.
31. Soviet organ sees confusion in US. *New York Times*. April 13, 1951:6.
32. *Pravda*. July 11, 1964:3.
33. Chinese reds blame US in cholera rise. *New York Times*. August 23, 1961:7.
34. Schaep B. US biological warfare: the 1981 Cuban dengue epidemic. *Covert Action*. 1982;17:28-31.
35. Seeley TD, Nowicki JW, Meselson M, Guillemin J, Akratanakul P. Yellow rain. *Sci Am*. 1985; 253(3):128-137.
36. WHO Group of Consultants. *Health Aspects of Chemical and Biological Weapons*. Geneva, Switzerland: World Health Organization; 1970.
37. Sims NA. *The Diplomacy of Biological Disarmament*. New York, NY: Plenum Press; 1983.
38. Becket B. *Weapons of Tomorrow*. New York, NY: Plenum Press; 1983.
39. Livingstone NC, Douglass DJD. *CBW: The Poor Man's Atom Bomb*. Cambridge, Mass: Institute for Foreign Policy Analysis Inc; 1984.
40. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. *Science*. 1994;266:1202-1208.
41. Smith RJ. Yeltsin blames '79 anthrax on germ warfare efforts. *Washington Post*. June 16, 1992:A1.
42. Rich V. Russia: anthrax in the Urals. *Lancet*. 1992;339:419-420.
43. Abramova FA, Grimberg LM, Yamposkaya OV, et al. Pathology of inhalation anthrax in 42 cases from the Sverdlovsk outbreak of 1979. *Proc Natl Acad Sci U S A*. 1993;90:2291-2294.
44. Leitenberg M. The biological weapons program of the former Soviet Union. *Biologicals*. 1993;21:187-191.
45. McCall S. A higher form of killing. *Proc US Naval Inst*. 1995;121:40-45.
46. United Nations, Security Council. *Report of the Secretary General on the Status of the Implementation of the Special Commission's Plan for the Ongoing Monitoring and Verification of Iraq's Compliance With Relevant Parts of Section C of Security Council Resolution 687 (1991)*. New York, NY: United Nations; October 11, 1995. Publication S/1995/864.
47. Zilinskas RA. Iraq's biological weapons: the past as future? *JAMA*. 1997;278:418-424.
48. Graham B. Military chiefs back anthrax inoculations; initiative would affect all of nation's forces. *Washington Post*. October 2, 1996:A1.
49. Weaver J. The town that was poisoned. *Congressional Record*. February 28, 1985;131:H901-H905.
50. Oregon Health Division. Salmonellosis in The Dalles. *Commun Dis Summ*. 1984;33:20.
51. Lon J. Rajneeshee dies in Indian commune. *Oregonian*. January 20, 1990:A1.
52. Török TJ. A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. *JAMA*. 1997;278:389-395.
53. Smith RJ. Japanese cult had network of front companies, investigators say. *Washington Post*. November 1, 1995:A8.
54. Daplan DE, Marshall A. *The Cult at the End of the World*. New York, NY: Crown Publishing Group; 1996.
55. Goldstein L. Saddam's biological warfare card. *Washington Post*. October 11, 1996:A24.
56. United Nations. *Fourth Review Conference of the Parties to the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction*. 1996; Geneva, Switzerland. Publication BW/CONF IV/9.
57. Chemical and Biological Arms Control Institute. *The Fourth Review Conference of the Biological and Toxin Weapons Convention: Doing No Harm*; February 1997; Alexandria, Va. Unpublished manuscript.